# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 26.01.2006 |
| Applicant's or agent's file reference<br>SPRV7PCT/P4422PC00 | **REPLY DUE** **within 2 month(s)** from the above date of mailing |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/FI2005/000064 | 31.01.2005 | 30.01.2004 |

International Patent Classification (IPC) or both national classification and IPC
C07K16/06

Applicant
SUOMEN PUNAINEN RISTI VERIPALVELU et al.

1. ☒ The written opinion established by the International Searching Authority:
   ☐ is ☒ is not
   considered to be a written opinion of the International Preliminary Examining Authority

2. This first report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☒ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   **When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   **How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   **Also:** For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   **If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 30.05.2006

| Name and mailing address of the international preliminary examining authority: | Authorized Officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Herrero, M<br>Telephone No. +49 89 2399-8542 |

**WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

International application No.
PCT/FI2005/000064



**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

   **Description, Pages**

   1-18 as published

   **Claims, Numbers**

   1-26 as published

   **Drawings, Sheets**

   1/1 as published

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

**Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 2-4, 6-16, 18-26 |
| | No: | Claims | 1, 5, 17 |
| Inventive step (IS) | Yes: | Claims | 11-12, 24-25 |
| | No: | Claims | 1-10, 13-23, 26 |
| Industrial applicability (IA) | Yes: | Claims | 1-26 |
| | No: | Claims | |

2. Citations and explanations:

**see separate sheet**

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

## SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 Reference is made to the following documents cited in the international search report:

D1: EP0413197
D2: WO99/64462 (also cited in the application)
D3: "Protein liquid Chromatography" Journal of Chromatography Library 2000, Vol. 61, Chapter 21, pages 766-768.
D4: WO03/100080
D5: Perosa, F. et al (1990) J. Immunological Methods **128**:9-16
D6: Troccoli, N.M. et al (1998) Biologicals **26**:321-329

2.2 The present IPEA agrees with the reasoned statement under Rule 43*bis*.1(a)(i) set forth in the written opinion of the ISA and consequently considers that:

(i) The application does not meet the criteria of Article 33(1) PCT, because the subject-matter of Claims 1, 5 and 17 is not new in the sense of Article 33(2) PCT.

D1 discloses a method for immunoglobulin purification comprising *inter allia* the steps of precipitating with caprylic acid, removing proteolytic activities from the precipitate with active charcoal, and subjecting the preparation to anion exchange chromatography and ultrafiltration (cf steps 1, 3, 4, and UF after step 5 in Figure 1). The disclosure of D1 would therefore appear to prejudice the novelty of present Claims 1, 5 and 17 (concerning Claim 17 see also item 2.3 below).

(ii) Having regard to the experimental results provided in the supporting description, the inventive contribution of the present disclosure seems to be in the combination of particular sequential precipitation and nanofiltration steps, as defined in present Claims 11-12 and 24-25, which enable the desirable filtration of small virus particles.

Nevertheless, the application does not meet the criteria of Article 33(1) PCT, because the subject-matter of Claims 1-10, 13-23 and 26 does not involve an inventive step in the sense of Article 33(3) PCT.

D2 discloses a method for immunoglobulin purification comprising e.g. the steps of precipitating with caprylic acid (cf page 8, lines 4-5), applying the supernatant of interest to an anion exchange resin and ultrafiltrating.

On page 768 D3 shows in Figure 21.1 a generic scheme for purification of antibodies comprising the steps of precipitation, ion exchange chromatography and nanofiltration.

D3 may be regarded as the closest prior art to the pursued method according to Claim 6.

Insofar as (i) the hereby claimed method only differs from the working approach of D3 by the specific pore size used and (ii) this particular nanofilter pore size is employed in the art to remove small viral particles (see D6), no inventive contribution appears to be associated with the method according to independent Claim 6. Moreover, the use of caprylic acid as precipitant in methods for purification of immunoglobulins is a standard technique. Therefore the person skilled in the art wanting to remove small viral particles from an antibody solution would seriously consider using a nanofilter with a pore size between 10-40 nm preceded by a standard precipitation with caprylic acid, thereby arriving at a method equivalent to the one of Claim 6

On the other hand, when considering the teachings of D3, independent Claim 18, as presently formulated, would only appear to describe a conventional method of nanofiltration. Problems associated with viruses having a particle size of about 20 nm are known in the art. Thus D6 teaches that it is desirable to remove virus particles with a size of about 20 nm from human intravenous immune globulin and discloses a method where 2,6 logs of such small viruses are removed with a 35 nm nanofilter. Hence, in the absence of the actual working steps defined in terms of technical features necessary to achieve the desirable result pursued in the claimed method (i.e. the features defined in Claims 24-25) Claim 18 cannot be regarded as inventive

(see in this regard the statements on page 3, lines 10-15 of the present description).

The use of caprylic acid in sequential combination with other precipitation aids in order to achieve a better purification result is known in the related art (see claim 10 of D4 and D5 as a whole). Therefore Claims 2-4 are only considered to involve preferred approaches which in the present context come within the scope of the customary practice followed by persons skilled in the art, contrary to the requirements of Art. 33(3) PCT.

Similarly, the preferred conditions regarding suitable pH, solution concentrations, pressure values, etc, reflected in dependent Clams 7-10, 13-16, 19-23 and 28 only appear to represent optional choices, within the common ranges used in the technical field (see e.g. D2), which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

2.3 No evidence is available suitable to ascertain whether the aqueous, virus-safe immunoglobulin solution comprising up to 250 g/l immunoglobulin and no detectable polymers or aggregates claimed *per se* in independent Claim 17 indeed represents novel and inventive subject-matter as required by Article 33(2) and (3) PCT. For the assessment of claims directed to products defined by their process of manufacture, on the question whether they are novel, no unified criteria exist in the PCT. The EPO, for example, does not recognize as novel the subject-matter of claims to known products defined in terms of a process of manufacture, however difficult or time consuming the employed technology may be, since it is considered that a product is not rendered novel merely by the fact that it is produced by means of a new process.

2.4 Further comments:

(i) Any amendment to be filed should be by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of

Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

(ii) In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

(iii) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply rather than be incorporated into the application, Article 34(2)(b) PCT.

## SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3-D6 is not mentioned in the description, nor are these documents identified therein.

2. With respect to Claim 5 it is noted that the use of expressions like "such as" (or "for example" or "preferably"...) has no limiting effect on the scope of said claim, i.e. the feature(s) following such expressions is (are) to be regarded as entirely optional (cf PCT Guidelines, C-III, 4.6).

## SECTION VIII

1. Although Claims 1 and 6 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only in respect of the terminology used for the features of that subject-matter (i.e. it

appears that Claim 6 could have been rendered dependent on Claim 1). The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.